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ORIGINAL REPORT

Cediranib, an Oral Inhibitor of Vascular Endothelial Growth Factor Receptor Kinases, Is an Active Drug in Recurrent Epithelial Ovarian, Fallopian Tube, and Peritoneal Cancer

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ABSTRACT

Purpose
Angiogenesis is important for epithelial ovarian cancer (EOC) growth, and blocking angiogenesis can lead to EOC regression. Cediranib is an oral tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptor (VEGFR) -1, VEGFR-2, VEGFR-3, and c-kit.

Patients and Methods
We conducted a phase II study of cediranib for recurrent EOC or peritoneal or fallopian tube cancer; cediranib was administered as a daily oral dose, and the original dose was 45 mg daily. Because of toxicities observed in the first 11 patients, the dose was lowered to 30 mg. Eligibility included ≤ two lines of chemotherapy for recurrence. End points included response rate (via Response Evaluation Criteria in Solid Tumors [RECIST] or modified Gynecological Cancer Intergroup CA-125), toxicity, progression-free survival (PFS), and overall survival (OS).

Results
Forty-seven patients were enrolled; 46 were treated. Clinical benefit rate (defined as complete response [CR] or partial response [PR], stable disease [SD] > 16 weeks, or CA-125 nonprogression > 16 weeks), which was the primary end point, was 30%; eight patients (17%; 95% CI, 7.6% to 30.8%) had a PR, six patients (13%; 95% CI, 4.8% to 25.7%) had SD, and there were no CRs. Eleven patients (23%) were removed from study because of toxicities before two cycles. Grade 3 toxicities (> 20% of patients) included hypertension (46%), fatigue (24%), and diarrhea (13%). Grade 2 hypothyroidism occurred in 43% of patients. Grade 4 toxicities included CNS hemorrhage (n = 1), hypertriglyceridemia/hypercholesterolemia/elevated lipase (n = 1), and dehydration/elevated creatinine (n = 1). No bowel perforations or fistulas occurred. Median PFS was 5.2 months, and median OS has not been reached; median follow-up time is 10.7 months.

Conclusion
Cediranib has activity in recurrent EOC, tubal cancer, and peritoneal cancer with predictable toxicities observed with other TKIs.

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INTRODUCTION

Epithelial ovarian cancer (EOC) occurs in an estimated 22,000 women per year in the United States.[1] Because most women with advanced EOC (stage III or IV) develop a recurrence despite up-front platinum- and taxane-based chemotherapy, newer biologic agents are needed to augment antitumor activity.[2-4] Options for recurrent EOC are expanding, and drugs that target vascular endothelial growth factor (VEGF) and the VEGF receptor (VEGFR) signaling pathways are active.[5,6] The addition of bevacizumab, an antibody to circulating VEGF, toup-front platinum- and taxane-based chemotherapy is currently undergoing testing in a randomized trial.

Cediranib (AZD2171; AstraZeneca, Wilmington, DE) is an oral, potent small-molecule inhibitor of several tyrosine kinases including VEGFR-1, VEGFR-2, VEGFR-3, and c-kit.[7,8] VEGFR-1 and VEGFR-2 are high-affinity receptors for VEGF that have associated tyrosine kinase activity[9-11]; VEGFR-2 seems to play a predominant role. VEGFR-3 is thought to be important for lymphangiogenesis.[12]

Phase I testing of cediranib showed a maximum-tolerated dose of 45 mg and anticancer activity.[13-18]

The purpose of this study was to assess activity and toxicity of cediranib in patients with either platinum-resistant or platinum-sensitive recurrent EOC, fallopian tube cancer, or peritoneal cancer.

PATIENTS AND METHODS

Study Design

This study was an open-label, phase II study of single-agent cediranib taken daily orally (PO) without interruption. Dosing began at 45 mg PO daily, but after 11 patients were enrolled, the dose of cediranib was decreased to 30 mg daily because of observed toxicities. This study was conducted at the Dana-Farber Cancer Institute, Brigham and Women's Hospital, Beth Israel Deaconess Hospital, and Massachusetts General Hospital, which are all members of the Dana-Farber/Harvard Cancer Center (Boston, MA); the study opened in September 2005, and accrual was completed in November 2008. The study was investigator initiated and was conducted using institutional programmatic funds; cediranib was provided by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute. The study and informed consent document were approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board and CTEP.

The primary objective was to determine the clinical benefit of cediranib in platinum-sensitive or platinum-resistant recurrent cancer based on either Response Evaluation Criteria in Solid Tumors (RECIST)[19] or Gynecological Cancer Intergroup (GCIG) modified CA-125 response.[20,21] Secondary objectives included toxicity assessment, progression-free survival (PFS), and overall survival (OS). One cycle equaled 28 days, and tumor assessment occurred every two cycles. Patients with either a partial response (PR) or a complete response (CR) by RECIST underwent confirmatory scanning 4 weeks later.[19] In the case of stable disease (SD) by RECIST, follow-up measurements must have met SD criteria for $\geq$ 16 weeks with scans performed every 8 weeks. Patients with both an elevated CA-125 and radiographically measurable cancer were evaluated using RECIST criteria. For patients evaluated using CA-125, CA-125 measurements were performed every 4 weeks. A CA-125 response occurred if a subsequent sample taken 4 weeks after initiating cediranib showed at least a 50% decrease without radiographic progression; confirmatory CA-125 was performed 4 weeks later. CA-125 progression was defined as doubling of the CA-125 level from baseline, and patients who had a stable (neither progression nor a response) CA-125 for more than 16 weeks were considered as having SD. Patients continued on study until cancer progression, excessive toxicities, or removal from study by either the patient or physician.

Study Population

This study initially allowed only patients in first relapse with a $\geq$ two-fold elevated CA-125 and no measurable cancer. Because of slow accrual, eligibility criteria were expanded to include the following: measurable cancer via RECIST criteria and receipt of up to two prior lines of therapy for recurrence. Other eligibility criteria were as follows: platinum-resistant or -sensitive EOC, peritoneal cancer, or fallopian tube cancer (progression of cancer $\geq$ 6 months after platinum-based chemotherapy was considered platinum sensitive, and cancers progressing $<$ 6 months from receipt of platinum-based chemotherapy were defined as platinum resistant), Eastern Cooperative Oncology Group performance status of $\leq$ 1, age $\geq$ 18 years, life expectancy of more than 6 months, and normal organ function (neutrophil count $\geq$ 1,500/μL, platelets $\geq$ 100,000/μL, hemoglobin $\geq$ 8 g/dL, total bilirubin and creatinine within institutional upper limit of normal, and AST and ALT $\leq$ 2.5$\times$ institutional upper limit of normal). Exclusion criteria were as follows: greater than +1 proteinuria, prior bevacizumab or drugs that inhibit VEGF or VEFGR, uncontrolled hypertension, therapeutic anticoagulation, prior malignancies that were recurrent or more than stage II cancer (except treated limited-stage basal cell or squamous cell carcinoma of the skin or in situ cancer of the breast or cervix), and use of any drug that interacted with CYP enzymes. Patients who had received prior anthracyclines underwent cardiac monitoring.

Toxicity and Efficacy

Toxicities were reported using the Common Terminology Criteria for Adverse Events version 3.0. Patients underwent a CBC count, chemistry panel, thyroid-stimulating hormone level, thyroxine, urinalysis, and CA-125 at the start of each cycle; these tests were repeated monthly. Patients were given a blood pressure monitoring device from AstraZeneca and recorded twice-daily self-measured blood pressure readings in a diary that was reviewed by the treating team each month. Patients were instructed to contact their treating team if their blood pressure was more than 150 mmHg systolic or more than 90 mmHg diastolic.

Dose Modifications and Delays

Dose levels were 45, 30, 20, and 10 mg; 10 mg was only allowed if approved by CTEP. Any episode of grade $\geq$ 3 nonhematologic or grade 4 hematologic or any grade 2 nonhematologic toxicity lasting more than 7 days attributable to cediranib resulted in holding treatment for up to 14 days until toxicity resolved to $\leq$ grade 1; cediranib was then restarted one dose lower.

Table 1. Demographics and Clinical Characteristics of the Patients Who Received Study Treatment

Demographic or Clinical Characteristic	No. of Patients (N =46)	%
Age, years		
Range	41-78	
Mean	57.4	
Median	56.5	
Platinum sensitivity		
PFI < 6 months	30	65
PFI ≥ 6 months	16	35
ECOG PS		
0	34	74
1	12	26
Race		
White (non-Hispanic)	45	98
Asian	1	2
Primary cancer diagnosis		
Ovarian cancer	40	87
Fallopian tube cancer	1	2
Peritoneal cancer	5	11
Histologic subtype		
Papillary serous	38	83
Endometrioid	1	2
Clear cell	3	6
Mixed type or other	4	9
Tumor grade		
1	1	2
2	0	0
2-3	6	13
3	39	85
Response assessment		
RECIST	36	78
CA-125	10	22
No. of prior therapies for recurrent cancer		
0	19	41
1	22	48
2	5	11
Prior history of hypertension		
Yes	6	13
No	40	87

Abbreviations: PFI, platinum-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; RECIST, Response Evaluation Criteria in Solid Tumors.

Patients were removed from study if grade 3 or 4 nonhematologic or grade 4 hematologic toxicities occurred that did not resolve to grade 0 to 2 after treating the patient at the lowest reduced dose level. Patients with grade 4 hypertension were removed from trial.

Statistics

The study design was a Simon two-stage optimum design. Clinical benefit was defined as one of the following: confirmed PR or CR by RECIST; SD by RECIST for more than 16 weeks; or GCIG CA-125 response or nonprogression for more than 16 weeks without progressive disease radiographically. Two separate strata were analyzed based on platinum resistance; if the true clinical benefit was found to be $\leq 5\%$ in patients with platinum-resistant cancer and $\leq 10\%$ in patients with platinum-sensitive cancer, cediranib would not be considered of further interest. For platinum-resistant patients, if at least one clinical response was observed in the first 13 patients, 14 additional patients were enrolled. The power to reject the null hypothesis that the true response rate was less than 5% in favor of the alternative hypothesis that the true rate was more than 20% was 80.11% at a type I error of 0.0416. For patients with platinum-sensitive recurrence, if at least two or more clinical responses were seen in the first 15 patients, 10 additional patients were enrolled. The power to reject the null hypothesis that the true response rate was less than 10% in favor of the alternative hypothesis that the true response rate was more than 30% was 80.17% at a type I error of 0.0328. Both cohorts met criteria for proceeding to the second stage; the study was closed after the platinum-resistant arm met its target during the second stage (four or more patients with clinical benefit).

The response rates and their 95% CIs were estimated based on the exact binomial distribution. Duration of response was measured from the time that measurement criteria were met for response until progression of cancer. PFS was defined as the duration of time from start of treatment to time of documented disease progression. OS was measured from date of start of study treatment to the date of death from any cause. PFS and OS were estimated using the Kaplan-Meier method.

RESULTS

Enrollment and Demographics

Forty-seven patients were enrolled onto the study; these patients represent the intent-to-treat (ITT) population. Median and mean follow-up times were 10.7 and 13.1 months, respectively. One patient never started therapy. Table 1 lists the demographics of the 46 patients who received treatment. Most patients were white (98%) and had ovarian cancer (87%), grade 3 papillary serous cancer (85%), no history of hypertension (87%), and no or one prior treatment for recurrence (89%). Sixty-five percent of patients (n = 30) had platinum-resistant recurrence, and 35% had platinum-sensitive recurrence (n = 16).

Anticancer Activity

Table 2 lists the overall response rates of this study based on platinum sensitivity. Overall clinical benefit for the ITT population was 30%; 17% patients achieved a PR representing the overall response rate. Thirteen percent of patients had SD. No patients had a CR. For the population of patients having clinical benefit, the mean duration of response was 3.9 months (range, 10 days to 11+ months). All patients experiencing clinical benefit had serous histology and $\leq$ one prior line for recurrence.

Twenty-one patients had progression of cancer as their best response to cediranib (45%; 95% CI, 30.1% to 60.0%). Eleven patients (23%; 95% CI, 12.3% to 38%) were withdrawn from therapy before obtaining a confirmed tumor response, and all were removed because of toxicities and failure to tolerate the drug. For these 11 patients, the median duration of cediranib was 49 days (range, 5 to 111 days). When the starting dose of cediranib is examined as a predictor of response, of the first 11 patients who received 45 mg PO daily, four had either a PR or SD (37%), whereas the remaining group of 36 patients starting at 30 mg had 10 responses (28%). For the first 11 patients who received 45 mg, the median time on this dose before dose reduction to 30 mg for toxicities was 22 days (range, 11 to 83 days). For the four patients starting on 45 mg who had clinical benefit, the median time before dose reduction was 30 days (range, 13 to 53 days).

Toxicities

Table 3 lists all drug-related toxicities experienced by at least 10% of patients and any grade 3 or 4 toxicities. The most common toxicities (all grades) were diarrhea (91%), fatigue (89%), hypertension (83%), hypothyroidism (56%), mucositis (50%), voice changes (46%), nausea (41%), headache (41%), abdominal pain (30%), proteinuria (24%), and vomiting (24%). Hypothyroidism was manifested most often by elevated thyroid-stimulating hormone and was grade 1 in 9%, grade 2 in 43%, and grade 3 in 4% of patients; grade 3 hypothyroidism toxicities included a patient who was admitted hypothyroid and hypothermic. No patient deaths occurred secondary to drug toxicity.

The most common $\geq$ grade 3 toxicities (occurring in $>$ 10% of patients) included hypertension (46%), fatigue (24%), and diarrhea (13%). One patient experienced hypercholesterolemia, elevated lipase, and hypertriglyceridemia (all grade 4) during the first cycle,

Table 2. Response Rates Based on the Degree of Platinum Sensitivity of the Cancer

Tumor Response	No. of Patients With Platinum-Resistant Cancer (n = 30)	No. of Patients With Platinum-Sensitive Cancer (n = 16)	All Patients (N = 47, intent-to-treat population)		
			No. of Patients	%	95% CI (%)
Complete response	0	0	0	0	0
Partial response	6*	2†	8	17	7.6 to 30.8
Stable disease	4‡	2†	6	13	4.8 to 25.7
Progressive cancer	15	6	21	45	30.1 to 60.0
Patients removed for toxicities before cancer assessment	5	6	11	23	12.3 to 38.0
Not evaluable (never received treatment)	—	—	1	2	0.05 to 11.3

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors.
*Response was determined via RECIST in five patients and via CA-125 in one patient.
†Response was determined via RECIST.
‡Response was determined via RECIST in three patients and via CA-125 in one patient.

Table 3. Grade 1 and 2 Toxicities Occurring in > 10% of Patients and Any Grade 3 and 4 Toxicities in Patients Who Received Study Drug (N = 46)

Toxicity	Grade 1		Grade 2		Grade 3		Grade 4		All Grades	
	No.	%	No.	%	No.	%	No.	%	No.	%
Diarrhea	20	43	16	35	6	13	0	0	42	91
Fatigue	16	35	14	30	11	24	0	0	41	89
Hypertension	7	15	10	22	21	46	0	0	38	83
Hypothyroidism	4	9	20	43	2	4	0	0	26	56
Mucositis	12	26	10	22	1	2	0	0	23	50
Voice changes	20	43	1	2	0	0	0	0	21	46
Nausea	13	28	4	9	2	4	0	0	19	41
Headache	17	37	1	2	1	2	0	0	19	41
Abdominal pain	8	17	5	11	1	2	0	0	14	30
Proteinuria	4	9	7	15	0	0	0	0	11	24
Vomiting	5	11	4	9	2	4	0	0	11	24
Anorexia	7	15	1	2	0	0	0	0	8	17
Weight loss	6	13	2	4	0	0	0	0	8	17
Hand-foot syndrome	3	7	3	7	0	0	0	0	6	13
Joint pain	4	9	1	2	1	2	0	0	6	13
Constipation	4	9	0	0	1	2	0	0	5	11
Dehydration	0	0	3	7	1	2	1	2	5	11
Dry skin	5	11	0	0	0	0	0	0	5	11
Muscle pain	4	9	1	2	0	0	0	0	5	11
Rash	5	11	0	0	0	0	0	0	5	11
ALT	3	7	2	4	0	0	0	0	5	11
Hyponatremia	1	2	0	0	3	7	0	0	4	9
Rectal pain/rectal hemorrhage	1	2	1	2	2	4	0	0	4	9
Creatinine	1	2	0	0	0	0	1	2	2	4
Hyperglycemia	0	0	1	2	1	2	0	0	2	4
CNS hemorrhage	0	0	0	0	0	0	1	2	1	2
Hypercholesterolemia, elevated lipase, hyperlipidemia	0	0	0	0	0	0	1	2	1	2

with levels of cholesterol of 604 mg/dL (normal, < 200 mg/dL), lipase of 526 U/L (normal, 0 to 60 U/L), and triglycerides of 5,292 mg/dL (normal, < 150 mg/dL). This patient had type 2 diabetes mellitus and prior hyperlipidemia (level of 1,200 mg/dL reported in 2002); cholesterol, lipid, and amylase levels before starting treatment were not available. Once toxicities were ≤ grade 1, cediranib was restarted at 20 mg, but 1 week later, the patient was removed from study with grade 2 hypertriglyceridemia. One patient developed grade 4 CNS hemorrhage in the setting of grade 2 hypertension; the patient was taken off study and recovered fully from this event. No episodes of cardiac toxicities, bowel perforations, fistulas, or grade 4 hypertension were observed.

Twenty-nine (63%) of 46 patients underwent a dose reduction of cediranib; of the first 11 patients who received 45 mg, eight (72%) had at least one dose reduction, and of the next 35 patients who started at 30 mg, 21 (60%) required a dose reduction. The most common reasons for a dose reduction (> 10% of patients) were fatigue (52%), diarrhea (31%), proteinuria (14%), hypertension (10%), and mucositis (10%); some patients had more than one toxicity leading to a dose reduction.

PFS and OS

PFS for the entire group of patients is shown in Figure 1A. Median PFS was 5.2 months; mean PFS was 4.6 months. Median PFS was identical for both platinum-resistant and platinum-sensitive recurrence groups. Eight (17%) of 47 patients were free of progression at 6 months. OS for the whole cohort is shown in Figure 1B; mean OS was 16.3 months, but median OS has not yet been reached.

DISCUSSION

As demonstrated in this study, cediranib has anticancer activity in patients with recurrent EOC, fallopian tube cancer, and peritoneal cancer with toxicities observed similar to other TKIs. In our study with an ITT population of 47 patients, we observed eight patients (17%) with a PR and six patients with SD (13%), resulting in an overall clinical benefit of 30%. Responses were observed in patients with platinum-resistant or platinum-sensitive cancer. The number of patients with SD observed in this study may be slightly inflated because of the manner in which we modified the GCIG criteria. Because these criteria lack a response of SD and only recognize a CA-125 response, we included those patients assessed using CA-125 as part of the clinical benefit who experienced more than 16 weeks of unchanged CA-125 as long as there was no evidence of RECIST progression; this expanded the definition of SD beyond the traditional definition of a CA-125 response and resulted in one additional patient being scored as having SD.

The observed toxicities included grade 3 hypertension (46%), grade 3 fatigue (24%), grade 3 diarrhea (13%), and grade 2 hypothyroidism (56%). A similar study to ours using cediranib for recurrent EOC[18] reported grade 3 hypertension in 33% and grade 3 fatigue in

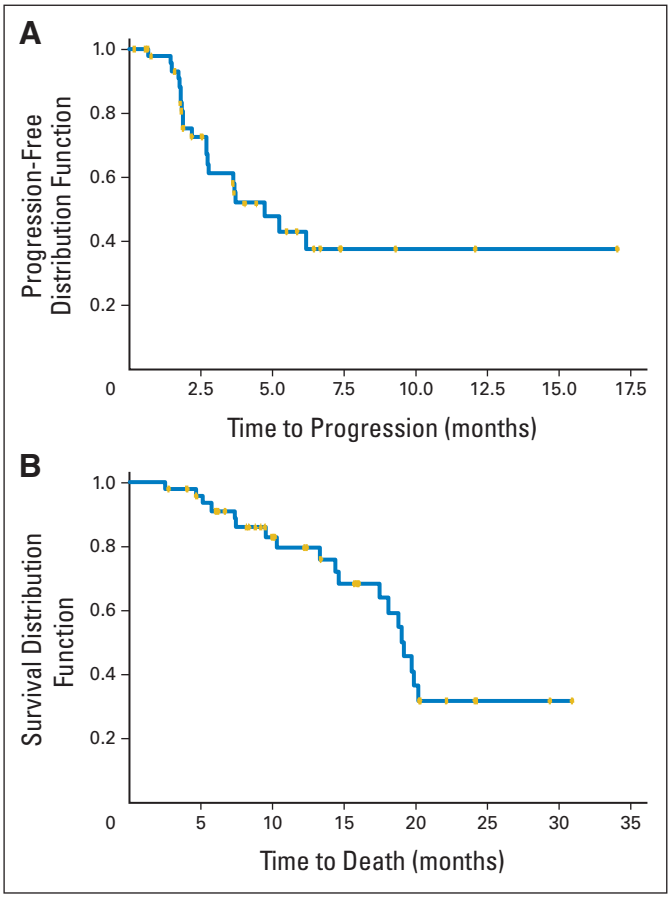

Fig 1. (A) Progression-free survival (PFS) and (B) overall survival (OS) of all patients. Median PFS was 5.2 months. Mean OS for the whole cohort was 16.3 months, and median OS has not yet been reached.

20% of patients. Our higher incidence of grade 3 hypertension may have resulted from patients' mandatory self-monitoring of their blood pressure. Our patients all received a blood pressure cuff as part of the study to self-monitor their blood pressure twice daily and report if their blood pressure was ≥ 150/90 mmHg. This close blood pressure monitoring may have detected more cases of clinically significant hypertension earlier. Hypertension, which is a common adverse effect of drugs that target VEGF or the VEGFRs may be a predictor for anticancer response. In colon cancer patients, hypertension associated with bevacizumab correlated with clinical outcome.[22] A similar observation was recently made in patients treated with combined anti–epidermal growth factor receptor therapy and bevacizumab for metastatic colon cancer; these patients had less hypertension and a poorer outcome.[23] In addition, sudden withdrawal of the drug can leave patients who are on several antihypertensive drugs susceptible to hypotension; hence, periodic breaks in treatment are logistically difficult. Hypothyroidism has been reported with other TKIs, and possible reported mechanisms include thyroid atrophy from reduction of vessel density.[24]

One unusual toxicity observed in this study was grade 4 hypercholesterolemia, hyperlipidemia, and elevated amylase; this occurred in a patient with type 2 diabetes mellitus with a past history of hyperlipidemia. The exact mechanism of these toxicities is unknown.

Because of the activity of cediranib in recurrent EOC, this agent should be considered during other phases of treatment. Cediranib is currently being tested in patients with their first recurrence of EOC who have platinum-sensitive cancer; International Collaborative Ovarian Neoplasm (ICON) 6 is testing the effects on OS, PFS, and quality of life of adding cediranib to platinum-based chemotherapy. Several features of cediranib also make this agent an attractive therapy for newly diagnosed EOC. The half-life of cediranib ranges from 12.4 to 35.7 hours, with an overall mean of 22 hours,[7] and because of this short half-life, cediranib could be used in the neoadjuvant setting. Data from a recently reported European Organization for the Research and Treatment of Cancer study showed equivalence of PFS comparing neoadjuvant chemotherapy followed by cytoreductive surgery and additional chemotherapy versus conventional treatment with cytoreductive surgery followed by platinum- and taxane-based chemotherapy.[25] However, addition of TKIs such as cediranib to chemotherapy may alter toxicities. In a recently published study of carboplatin/paclitaxel with or without cediranib for advanced non–small-cell lung cancer, patients receiving cediranib experienced higher rates and severity of hypertension, fatigue, GI toxicities (anorexia, diarrhea, and mucositis), and neutropenia compared with patients receiving carboplatin and paclitaxel alone[26]; other toxicities attributable to chemotherapy did not occur at a greater rate or severity than expected.

Bevacizumab has been studied in recurrent EOC. Cannistra et al[5] demonstrated an overall response rate of 18% and a median PFS of 4.4 months in patients with platinum-resistant cancer who experienced progression with either liposomal doxorubicin or topotecan. The median response duration was 4.2 months. Burger et al[6] studied bevacizumab in patients with both platinum-sensitive and platinum-resistant recurrence and observed an overall response rate of 21% and a median PFS of 4.7 months; median response duration was 10 months. Our study showed an overall response rate of 17% and observed median PFS of 5.2 months, which compares favorably to both of these single-agent bevacizumab trials. These anticancer responses observed in platinum-resistant EOC with both cediranib and bevacizumab[6] suggest that anti-VEGF therapies can circumvent pathways of platinum resistance. However, toxicity profiles do differ between bevacizumab and cediranib; ≥ grade 3 hypertension occurred in 11.3% of patients in the study by Burger et al,[6] 9% of patients in the study by Cannistra et al,[5] and 46% of patients in our study. None of the patients in our cediranib study developed a bowel perforation, whereas bevacizumab studies have documented perforation rates of up to 11%[5]; however, this toxicity must be carefully monitored in TKI studies as well. Other inhibitors of VEGF and VEGFR signaling are currently being tested in relapsed EOC (ie, vandetanib, IMC1121-B, BIBF 1120, CP-547632, and sunitinib). As results emerge from these studies, choice of drug will not only depend on efficacy but also on cost (both financial and quality-of-life costs) and where the drug is being used in a patient's treatment. One weakness of our study is that we did not include patient-reported outcomes, and randomized trials of these drugs should include patient-reported outcomes to assess effects on quality of life.

In summary, cediranib is an active drug in recurrent ovarian cancer with significant toxicities that are observed with other TKIs. Cediranib is currently being tested combined with chemotherapy and as a maintenance drug in platinum-sensitive recurrent EOC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Anna Berkenblit, Wyeth (C); Richard T. Penson, Genentech (C) **Consultant or Advisory Role:** Ursula A. Matulonis, Genentech (C) **Stock Ownership:** Anna Berkenblit, Wyeth **Honoraria:** Richard T. Penson, Abbott Laboratories **Research Funding:** Ursula A. Matulonis, Genentech; Richard T. Penson, Genentech, DARA BioSciences, Eli Lilly, CuraGen, ImClone Systems, Endocyte **Expert Testimony:** None **Other Remuneration:** None

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